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(54) Title: ORAL CONTRACEPTIVE PREPARATION HAVING A FIRST PHASE COMPRISING PROGESTIN/ESTROGEN AND A SECOND PHASE COMPRISING PROGESTIN

(57) Abstract

This invention provides a method of contraception which comprises administering to a female of child bearing age for 28 days per menstrual cycle a combination of a progestin at a daily dosage equivalent to 30–150 μg levornorgestrel and an estrogen at a daily dosage equivalent to 10–20 μg ethinyl estradiol for 23–25 days beginning on day 1 of the menstrual cycle, followed by administering a progestin at a daily dosage equivalent to 10–100 μg levornorgestrel for 3–5 days.

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ORAL CONTRACEPTIVE PREPARATION HAVING A FIRST PHASE COMPRISING PROGESTIN/ESTROGEN AND A SECOND PHASE COMPRISING PROGESTIN

BACKGROUND OF THE INVENTION

The vast majority of oral contraceptives consist of a combination of a progestin and estrogen that are administered concurrently for 21 days followed either by a 7 day pill free interval or by the administration of a placebo for 7 days in each 28 day cycle. The most important aspects of a successful oral contraceptive product are effective contraception, good cycle control (absence of spotting and breakthrough bleeding and occurrence of withdrawal bleeding), and minimal side effects. Combination oral contraceptives have traditionally acted by suppression of gonadotropins. In addition, it appears that the progestin component is primarily responsible for contraceptive efficacy through inhibition of ovulation, and other peripheral effects which include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation). The estrogenic component intensifies the anovulatory effect of the progestin, and is also important for maintaining cycle control.

Since the introduction of oral contraceptives (OCs) over a quarter-century ago, research has been directed toward developing preparations that minimize the potential for side effects while maintaining efficacy and normal menstrual patterns. The first-generation OCs contained more progestin and estrogen than was necessary to prevent conception. Adverse hemostatic and metabolic changes, clinical problems, and side effects were associated with these high-dose preparations. In 1978, the World Health Organization (WHO) recommended that the focus of OC research should be the development of products containing the lowest possible dose levels of estrogen and progestin.

The first reductions in steroid content in a combination pill were focused on estrogen because it, rather than progestin, was thought to be related to the most serious side effects. Reduction in progestin content followed, as evidence mounted that lowering progestin intake might lower the risk of cardiovascular complications such as stroke and ischemic heart disease. [Kay CR, Am J Obstet Gynecol 142:762 (1982)]. However, this evidence was not as clear as that implicating estrogen in thromboembolic disorders. [Inman WHW, Br Med J 2:203 (1970); Stolley PD, Am J Epidemiol 102:197 (1975)]. The need for a balance between estrogens and progestins to minimize adverse effects on carbohydrate metabolism and on lipid and lipoprotein levels was also recognized. [Bradley DD, N Engl J Med 299:17 (1978); Wynn V, Lancet 1:1045 (1979)]. Researchers then found that the synergistic action between progestin and

estrogen in a balanced ratio successfully inhibited ovulation at low levels of both components.

Research into low-dose progestins was advanced significantly by the development of norgestrel (Ng) and levonorgestrel (LNg). Levonorgestrel is the biologically active moiety of racemic norgestrel. It is strongly progestational, has no inherent estrogenic activity, is antiestrogenic, and possesses good biologic activity. The contraceptive effects of levonorgestrel are manifested throughout the hypothalamic-pituitary-gonadal-target organ axis.

Ethinyl estradiol (EE) is the estrogen most frequently used in combination OCs. In attempts to fulfill the WHO objective, the dosage of EE in marketed OC formulations has been steadily reduced from that found in earlier OCs. Thromboembolic mortality decreased when the amount of synthetic estrogen in OC formulations was reduced from 100 μg to 50 μg. Subsequently, a significant reduction in fatal myocardial infarctions was reported for women using OCs with 30 μg of EE rather than 50 μg of EE. [Meade TW, Br Med J 280:1157 (1980)].

In keeping with the goal of reducing the total steroidal dosage, while maintaining contraceptive efficacy, good cycle control, and minimizing side effects, numerous regimens have been developed in which the progestin/estrogen combination is administered either as a fixed dosage combination (monophasic) or as biphasic or triphasic regimens in which the dosage of the combination is varied either once or twice throughout the menstrual cycle. In these regimens, the progestin/estrogen combination is typically administered for 21 days followed by either a 7-day pill free period or the administration of a non-contraceptive placebo (or iron supplement) for 7 days. In these regimens, 3-ketodesogestrel (3-KDSG), desogestrel (DSG), levonorgestrel (LNg), gestodene (GTD), norgestrel (NG), and norethindrone (NE) are typically used as the progestin while ethinyl estradiol (EE); 17β-estradiol, and mestranol are typically the estrogenic components.

Several examples of attempts at reducing the total steroidal dosage by using bridged or 24-day regimens are provided below.

De Jager (European Patent Application 368,373 A) discloses 22-30 day bridged regimens consisting of the administration of 20-22 (preferrably 21) days of a progestin/estrogen combination followed by 2-10 (preferrably 7) days of a progestin. Specifically disclosed regimens include (a) a combination of 150 μg DSG and 2.0 mg 17β-estradiol for 21 days, followed by 30 μg desogestrel for 7 days; (b) a combination of 150 μg DSG and 30 μg EE for 21 days, followed by 30 μg desogestrel for 7 days; (c) a combination of 50 μg DSG and 3 mg 17β-estradiol for 7 days, followed by a

combination of 150 μg DSG and 2 mg 17β-estradiol for 14 days, followed by 30 μg DSG for 7 days; (d) a combination of 50 μg DSG and 35 μg EE for 7 days, followed by a combination of 150 μg DSG and 30 μg EE for 14 days, followed by 30 μg DSG for 7 days; (e) a combination of 50 μg DSG and 3 mg 17β-estradiol for 7 days, followed by a combination of 100 μg DSG and 2 mg 17β-estradiol for 7 days, followed by a combination of 150 μg DSG and 1.5 mg 17β-estradiol for 7 days, followed by 30 μg DSG for 7 days; (f) a combination of 50 μg DSG and 3 mg 17β-estradiol for 7 days, followed by a combination of 100 μg DSG and 2 mg 17β-estradiol for 7 days, followed by a combination of 150 μg DSG and 1.5 mg 17β-estradiol for 8 days, followed by 30 μg DSG for 6 days; (g) a combination of 50 μg LNG and 2 mg 17β-estradiol for 11 days, followed by a combination of 150 μg LNG and 2 mg 17β-estradiol for 11 days, followed by 125 μg LNg for 2 days; and (h) a combination of 50 μg LNG and 2 mg 17β-estradiol for 6 days, followed by a combination of 75 μg LNG and 2.5 mg 17β-estradiol for 5 days, followed by a combination of 125 μg LNG and 2 mg 17β-estradiol for 10 days, followed by 70 μg LNg for 2 days, followed by 50 μg LNg for 2 days.

Endrikat (PCT Publication WO 97/23228) discloses bridged regimens consisting of the squential administration of an ovulation inhibiting dose of a progestin for at least 28 days and a natural estrogen during the last 5-10 days of the at least 28 day sequential administration. A preferred contraceptive kit consists of 28 daily dosage units with a first phase having 18-23 daily dosage units of a progestin and a second phase having 5-10 daily dosage units of a prigestin in combination with a natural estrogen. Specific disclosed regimens include: (a) administration of 100 μg LNg for 28 days, with 2.5 mg 17β-estradiol concomitantly adminsistered for the last 10 days of the 28-day administration; (b) administration of 100 μg LNg for 28 days, with 2.5 mg 17β-estradiol concomitantly adminsistered for the last 8 days of the 28-day administration; (c) administration of 100 μg LNg for 56 days, with 2.5 mg 17β-estradiol concomitantly adminsistered for the last 10 days of the 56-day administration; (d) administration of 100 μg LNg for 84 days, with 2.5 mg 17β-estradiol concomitantly adminsistered for the last 10 days of the 84-day administration; and equivalent regimens using 75 μg GTD as the progestin.

Erlich (German Patent DE 4,104,385 C1 and U.S. Patent 5,280,023) discloses sequential contraceptive regimens consisting of the administration of an estrogen which effects a disturbance of follicle stimulation, followed by the administration of a combination of a progestin/estrogen in a dose at least adequate to inhibit ovulation. The regimen is administered for a total of 28 days per cycle. It is preferred that the estrogen is administered for 5-14 days per cycle and the progestin/estrogen combination

is administered for 23-14 days per cycle, so that the total administration is for 28 days per cycle. Specific regimens include (a) 4 mg estradiol for 7 days followed by 21 days of the combination of 1 mg norethisterone acetate and 4 mg estradiol; (b) 2 mg estradiol valerate for 7 days followed by 21 days of the combination of 2 mg chlormadinone acetate and 4 mg estradiol valerate; and (c) 20 μg EE followed by 18 days of the combination of 150 μg LNg and 20 μg EE. Regimen (c) in Erlich provides a total steroidal load of 2.7 mg of LNg and 560 μg EE per 28 day cycle.

Lachnit (PCT Publication WO 95/26730) discloses bridged regimens consisting of the administration of a combination of a progestin/estrogen combination (50 - 125 μg LNg and 10 - 40 μg EE) for the first 23-24 days of the menstrual cycle followed by the administration of an estrogen (2 - 40 μg EE) for 4-10 days for a total administration of at least 28 days per cycle. The use of 100 - 300 μg drospirenone and 10 - 40 μg EE as the 23-24 day progestin/estrogen combination is disclosed. Lachnit also discloses a triphasic plus bridging regimen (4-9 days, 4-9 days, 9-13 days, and 28 days for the three phases and estrogen phase, respectively) in which a combination of 50 μg LNg and 20 μg EE are administered in the first phase, a combination of 75 μg LNg and 25 μg EE are administered in the second phase, a combination of 100 μg LNg and 20 μg EE are administered in the third phase, and 10 μg EE is administered in the estrogen phase. Other progestins disclosed include GTD, DSG, 3-KDSG, DRSP, cyproterone acetate, norgestimate, and norethisterone.

Moore (DE 4313926 A1) discloses bridged triphasic regimens consisting of the administration of a combination of 10 - 50 μg LNg and 5 - 20 μg EE from days 1-7 of the menstrual cycle; of 50 - 75 μg LNg and 5 - 20 μg EE from days 8-14 of the menstrual cycle; of 75 - 125 μg LNg and 5 - 20 μg EE from days 15-21 of the menstrual cycle; and 5 - 20 μg EE from days 22-28 of the menstrual cycle.

Spona (U.S. Patent 5,583,129 and PCT Publication WO 95/17194) discloses contraceptive regimens which consist of the administration of a combinaton of a progestin (50 - 75 μg GTD, 75 - 125 μg LNg, 60 - 150 μg DSG, 60 - 150 μg 3-KDSG, 100 - 300 μg DRSP, 100 - 200 μg cyproterone acetate, 200 - 300 μg norgestimate, or >350 - 750 μg norethisterone) and an estrogen (15 - 20 μg EE or 2 - 6 mg 17β-estradiol) for 23-24 days per cycle.

Upton (EP Patent Specification 253,607 B1) teaches the use of low dose progestin/estrogen combinations for combined hormone replacement therapy and contraception in climacteric women. Climacteric women are defined in Upton as pre-menopausal women around 40 years of age whose hormone levels are waning. The climacteric woman still ovulates (albeit may have irregular ovulation), but she still experiences many of the symptoms of the hypoestrogenic menopausal woman, such as

insomnia, hot flushes, and irritability. Upton teaches the administration of a 23-26 day monophasic regimen of progestin/estrogen followed by a pill free or placebo interval of 2-5 days; with 24 days of progestin/estrogen administration followed by a 4-day pill free or placebo administration being preferred. Upton teaches the use of a progestin selected from 25 - 100 μg LNg, 10 - 70 μg GTD, 25 - 100 μg DSG, 25 - 100 μg 3-KDSG, and 85 - 350 μg NE used in combination with an estrogen selected from 500 - 2000 μg 17β-estradiol, 8 - 30 μg EE, and 15 - 60 μg mestranol. Based on relative potencies, Upton teaches that a dose of 75 μg LNg is equivalent to 35 μg of GTD, 75 μg of 3-KDSG or DSG, and 250 μg NE and that a dose of 1000 μg of 17β-estradiol is equivalent to a dose of 15 μg EE and 30 μg mestranol. Upton also teaches that NG may be substituted for LNg, but at twice the dose.

Bergink (U.S. Patent 5,262,408) discloses a 24 day triphasic combination regimen in which the first 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 100 μg DSG and an estrogen at a daily dosage equivalent to 25 μg EE, the second 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 125 μg DSG and an estrogen at a daily dosage equivalent to 20 μg EE, and the third 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 50 μg DSG and an estrogen at a daily dosage equivalent to 20 μg EE. It is preferred that the three phases be 8 days each. Following the 24 day contraceptive steroid administration, a placebo may be administered for 4 days, the 4 day interval may be pill free, or a progestin at a dosage equivalent to 25-35 μg DSG may be administered.

DESCRIPTION OF THE INVENTION

This invention provides a progestin bridged combination progestin/estrogen oral contraceptive regimen for females of child-bearing age that provides effective contraception, good cycle control, and minimal side effects while greatly reducing the total contraceptive steroid administered per 28-day cycle. To achieve the substantial reduction in the total contraceptive steroid administered per cycle while maintaining good cycle control, the low dose progestin/estrogen combination is administered for 23-25-days per cycle followed by the administration of a progestin for the remaining 3-5 days of the cycle. Administration of the contraceptive progestin/estrogen combination is begun on the first day of menses (day 1), and continued for 23-25 consecutive days. Following the 23-25-day administration period, a progestin is administered for 3-5 days to assist in maintaining good cycle control. The total administration during each cycle is 28 days.

More particularly, this invention provides a method of contraception which comprises administering to a female of child bearing age a combination of a progestin at a daily dosage equivalent in progestational activity to 40-150 μg levonorgestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle. Following the 23-25-day period, a progestin at a daily dosage equivalent to 10-100 μg levonorgestrel is administered for 3-5 days. The total administration during each cycle is 28 days.

Preferred progestins include, but are not limited to levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethisterone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, and drospirenone. It is more preferred that the progestin is levonorgestrel. When levonorgestrel is used as the progestin during the first 23-25 days of the cycle, it is preferred that the daily dosage of levonorgestrel is 30-150 μg, with 50-100 μg being more preferred, and 90 μg being most preferred. When levonorgestrel is used as the progestin during the last 3-5 days of the cycle, it is preferred that the daily dosage be 10-100 μg, with 20-50 μg levonorgestrel being more preferred, and 37.5 μg most preferred. Preferred dosages of the preferred progestins are provided in the table below.

PREFERRED DAILY DOSAGE RANGES

Progestin	First 23-25 Cycle Days	Last 3-5 Cycle Days
Levonorgestrel	30-150 μg	10-100 μg
Norgestrel	60-300 μg	20-200 μg
Desogestrel	45-225 μg	15-150 μg
3-Ketodesogestrel	45-225 μg	15-150 μg
Norethindrone	200 μg - 1 mg	65-650 μg
Norethisterone Acetate	200 μg - 1 mg	65-650 μg
Gestodene	20-115 μg	7.5-75 μg
Norgestimate	75-375 μg	25-250 μg
Osaterone	250 μg - 2.5 mg	100 μg - 1.5 mg
Trimegestone	75-375 μg	25-250 μg
Dienogest	500 μg - 3.75 mg	100 μg - 2.5 mg
Drospirenone	500 μg - 3.75 mg	100 μg - 2.5 mg
Cyproterone Acetate	450 μg - 2.5 mg	150 μg - 1.5 mg

Preferred estrogens include, but are not limited to ethinyl estradiol; 17β-estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol; with ethinyl estradiol being more preferred. When ethinyl estradiol is used as the estrogen the preferred daily dosage is 10-20 μg, with 15 μg being more preferred. When 17β-estradiol is used as the estrogen, it is preferred that the daily dosage of 17β-estradiol is 1-3 μg. Preferred salts of estrone include, but are not limited to the sodium and piperate salt. When conjugated estrogens, USP are used as the estrogen, it is preferred that the daily dosage is 0.3-5 mg, with a daily dose of 1.25 mg conjugated estrogens, USP being equivalent to a daily dose of 15 μg ethinyl estradiol.

It is preferred that the progestin/estrogen combination be administered for 24 days beginning on day 1 of the menstrual cycle, and following this 24-day period, it is preferred that the progestin be administered for 4 days.

The following daily dosages of a combination of levonorgestrel and ethinyl estradiol are preferred for contraception when administered for 23-25 consecutive days beginning on the first day of menses, followed by the administration of levonorgestrel for 3-5 days. The total administration during each cycle is 28 days.

PREFERRED DAILY DOSAGES

	First 23-25 Cycle Days		Last 3-5 Cycle Days
Regimen	Levonorgestrel	Ethinyl Estradiol	Levonorgestrel
A	100 μg	15 μg	20-50 μg
B	90 μg	15 μg	20-50 μg
C	75 μg	15 μg	20-50 μg
D	60 μg	15 μg	20-50 μg
E	50 μg	15 μg	20-50 μg
F	40 μg	15 μg	20-50 μg
G	100 μg	10 μg	10-40 μg
H	90 μg	10 μg	10-40 μg
I	75 μg	10 μg	10-40 μg
J	60 μg	10 μg	10-40 μg
K	50 μg	10 μg	10-40 μg
L	40 μg	10 μg	10-40 μg

The following daily dosages of a combination of levonorgestrel and ethinyl estradiol are more preferred for contraception when administered for 24 consecutive days beginning on the first day of menses, followed by the administration of

levonorgestrel for 4 days. The total administration during each cycle is 28 days. Of the regimens listed below, Regimens M-O are more preferred, with Regimen N being most preferred.

MORE PREFERRED DAILY DOSAGES

	First 24 Cycle Days		Last 4 Cycle Days
Regimen	Levonorgestrel	Ethinyl Estradiol	Levonorgestrel
M	75 µg	15 µg	37.5 µg
N	90 µg	15 µg	37.5 µg
O	100 µg	15 µg	37.5 µg
P	50 µg	10 µg	25 µg
Q	60 µg	15 µg	37.5 µg
R	75 µg	10 µg	25 µg
S	40 µg	15 µg	37.5 µg

For administration during the first 23-25 days of the menstrual cycle, it is preferred that the combination progestin/estrogen contraceptive be administered in unit dosage form i.e., tablet or pill, with each unit providing the entire daily dosage. It is preferred that the progestin and estrogen are admixed together in the same dosage unit. Such dosage units can be prepared by conventional methodology that is well known to one skilled in the art. In each dosage unit, the contraceptively active progestin and estrogen are combined with excipients, vehicles, pharmaceutically acceptable carriers, and colorants. For example, the following illustrates an acceptable composition of a contraceptive progestin/estrogen combination of this invention.

EXAMPLE 1

Levonorgestrel, 75 µg
Ethinyl estradiol, 15 µg
Microcrystaline Cellulose
Lactose, NF, Spray Dried
Polacrillin Potassium, NF
Magnesium Stearate
Opadry Pink
Polyethylene Glycol, 1500, Flakes
Water, Purified, USP
Wax E (Pharma)

For administration during the last 3-5 days of the menstrual cycle, it is preferred that the progestin be administered in unit dosage form i.e., tablet or pill, with each unit providing the entire daily dosage. Such dosage units can be prepared by conventional methodology that is well known to one skilled in the art. In each dosage unit, the estrogen is combined with excipients, vehicles, pharmaceutically acceptable carriers, and colorants. For example, the following illustrates an acceptable estrogen composition of this invention.

EXAMPLE 2

Levonorgestrel, 37.5 µg
Microcrystaline Cellulose
Lactose, NF, Spray Dried
Polacrillin Potassium, NF
Magnesium Stearate
Opadry Pink
Polyethylene Glycol, 1500, Flakes
Water, Purified, USP
Wax E (Pharma)

This invention also provides a contraceptive kit adapted for daily oral administration which comprises a total of 28 separate dosage units. In this kit, 23-25 dosage units each consisting of a combination of progestin at a daily dosage equivalent in progestational activity to 30-150 µg levonorgestrel and an estrogen at a daily dosage equivalent to 10-20 µg ethinyl estradiol. The remaining 3-5 dosage units contain an progestin at a daily dosage equivalent to 10-100 µg levonorgestrel. The daily dosage arrangements are preferably arranged in a blister pack or in a dial pack type tablet dispenser. Specific referred progestins and estrogens and the specifically preferred dosages of each combination dosage unit are described above.

WHAT IS CLAIMED IS:

1. A method of contraception which comprises administering to a female of child bearing age a combination of a progestin at a daily dosage equivalent to 30-150 μg levonorgestrel and an estrogen at a daily dosage equivalent to 10-20 μg ethinyl estradiol for 23-25 days per menstrual cycle beginning on day 1 of the menstrual cycle; wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days, followed by the administration of a progestin at a daily dosage equivalent to 10-100 μg levonorgestrel for 3-5 days; wherein the same dosage of the progestin is administered in each of the 3-5 days; such that the number of days of administration of the progestin and estrogen combination plus the number of days of administration of progestin is equal to 28 per menstrual cycle.

2. The method according to claim 1, wherein the combination of progestin and estrogen is administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle, followed by the administration of progestin for 4 days per menstrual cycle.

3. The method according to claim 1 or 2, wherein the progestin is selected from the group consisting of levonorgestrel, norgestrel, desogestrel, 3-keto-desogestrel, norethindrone, gestodene, norethisterone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, and drospirenone.

4. The method according to claim 1, 2 or 3, wherein the estrogen is selected from the group consisting of ethinyl estradiol; 17β-estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.

5. The method according to any one of claims 1 to 4, wherein the progestin is levonorgestrel.

6. The method according to any one of claims 1 to 5, wherein the estrogen is ethinyl estradiol.

7. The method according to any one of claims 1 to 6, wherein levonorgestrel and ethinyl estradiol are administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle, followed by the administration of levonorgestrel for 4 days per menstrual cycle.

8. The method according to claim 7, wherein the daily dosage of levonorgestrel administered during the first 24 days of the menstrual cycle is 50-100 μg and 20-50 μg during the last 4 days of the menstrual cycle.

9. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 90 μg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μg; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μg.

10. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 75 μg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μg; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μg.

11. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 100 μg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μg; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μg.

12. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 50 μg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 10 μg; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 25 μg.

13. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 60 μg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μg; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μg.

14. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 75 μg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 10 μg; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 25 μg.

15. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 40 μg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μg;and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μg.

16. A contraceptive kit adapted for daily oral administration which comprises 28 separate dosage units, 23-25 of said dosage units each containing a combination of progestin at a daily dosage equivalent to 30-150 μg levonorgestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol, wherein each of the 23-25 dosage units contains the same dosage of progestin and estrogen; and 3-5 of said dosage units containing an progestin at a daily dosage equivalent to 10-100 μg levonorgestrel, wherein each of the 3-5 dosage units contains the same dosage of progestin.

17. The contraceptive kit according to claim 16, wherein 24 of the 28 dosage units contain the progestin and estrogen combination, and 4 of the dosage units are estrogen free.

18. The contraceptive kit according to claim 16 or 17, wherein the progestin is selected from the group consisting of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethisterone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, and drospirenone, and the estrogen is selected from the group consisting of ethinyl estradiol; 17β-estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.

19. The contraceptive kit according to claim 16, 17 or 18 wherein the estrogen is ethinyl estradiol and the progestin is levonorgestrel.

20. The contraceptive kit according to claim 19 wherein the dosage of levonorgestrel in each of the estrogen containing dosage units is 50-100 μg, and in the estrogen free dosage units is 20-50 μg.

21. The contraceptive kit according to claim 20 wherein the dosage of ethinyl estradiol in each progestin containing dosage unit is 15 μg and the dosage of levonorgestrel in each estrogen containing dosage unit is 90 μg and in each estrogen free dosage unit is 37.5 μg.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 98/18850

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 368 373 A (AKZO N.V.) 16 May 1990 cited in the application see examples I-IV see claims 1-10,12-17 see page 2, line 51 - page 3, line 42	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 December 1998	17/12/1998

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 4287989 A	26-04-1990
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